AMENDMENTS TO THE CLAIMS

1-57. (Canceled)

58. (Previously presented) A method of designing a non-cytotoxic toxin conjugate for inhibition or reduction of exocytic fusion in a target cell, comprising:

(a) identifying an agonist that increases exocytic fusion in said target cell; and

(b) preparing an agent, said agent comprising:

(i) a targeting moiety that binds the agent to a binding site on said target cell, said binding site undergoes endocytosis to be incorporated into an endosome within the target cell, and wherein the targeting moiety is an agonist identifiable by step (a);

(ii) a non-cytotoxic protease or a fragment thereof, said protease or protease fragment is capable of cleaving a protein of the exocytic fusion apparatus of said target cell; and

(iii) a translocation domain that translocates the protease or protease fragment from within the endosome, across the endosomal membrane, and into the cytosol of the target cell.

59. (Withdrawn) A method of designing a non-cytotoxic toxin conjugate for inhibition or reduction of exocytic fusion in a target cell, comprising:

(a) identifying an agonist that increases exocytic fusion in said target cell; and

(b) preparing an agent, said agent comprising:

(i) a targeting moiety that binds the agent to a binding site on said target cell, said binding site undergoes endocytosis to be incorporated into an endosome within the target cell, and wherein the targeting moiety is an agonist identifiable by step (a);

(ii) a DNA sequence encoding a non-cytotoxic protease or a fragment thereof, said DNA sequence is expressible in the target cell and when so expressed provides a

protease or protease fragment capable of cleaving a protein of the exocytic fusion apparatus of said target cell; and

(iii) a translocation domain that translocates the DNA sequence encoding the protease or protease fragment from within the endosome, across the endosomal membrane, and into the cytosol of the target cell.

60. (Previously presented) A method according to Claim 58, wherein said step of identifying an agonist comprises identifying an agonist that is suitable for re-targeting the non-cytotoxic protease or a fragment thereof to a target cell, comprising:

(a) identifying a putative agonist molecule;

(b) contacting the target cell with said putative agonist molecule; and

(c) confirming said putative agonist molecule is an agonist by identifying an increase in exocytic fusion in the target cell when said molecule is present compared with when said molecule is absent.

61. (Previously presented) A method according to Claim 60, comprising the step of confirming that the putative agonist molecule or agonist is capable of being combined with a non-cytotoxic protease or a fragment thereof, or a DNA sequence encoding said protease or the fragment thereof, to form an agent of the present invention.

62. (Previously presented) A method according to Claim 60, comprising the step of confirming that said putative agonist molecule or agonist binds to a binding site on the target cell, said binding site is susceptible to receptor-mediated endocytosis.

63. (Previously presented) A method according to Claim 60, comprising the step of confirming that said putative agonist molecule or agonist is able to deliver said non-cytotoxic protease or fragment thereof, or a DNA sequence encoding said protease or the fragment thereof, into the cytosol of a target cell.

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64. (Previously presented) A method according to Claim 60, wherein step (c) comprises detecting an increase in secretion from the target cell when agonist is present compared with when said agonist is absent.

65. (Previously presented) A method according to Claim 64, wherein said detecting is performed by an assay employing chromatography, mass spectroscopy, or fluorescence.

66. (Previously presented) A method according to Claim 64, wherein said detecting is performed by an assay employing ELISA/EIA/RIA techniques, or radio-tracer techniques.

67. (Previously presented) A method according to Claim 60, wherein step (c) comprises detecting an increase in the concentration of a cell membrane protein expressed at the surface of the target cell when agonist is present compared with when said agonist is absent.

68. (Previously presented) A method according to Claim 67, wherein the cell membrane protein is a cell receptor protein, and the method comprises detecting an increase in the concentration of said receptor protein expressed at the surface of the target cell when agonist is present compared with when said agonist is absent.

69. (Previously presented) A method according to Claim 67, wherein said detecting is performed by an assay employing immuno-histochemistry, flow cytometry, western blotting of isolated plasma membrane cell fractions, fluorescent-ligand binding techniques, or radio-ligand binding techniques.

70. (Previously presented) A method according to Claim 67, wherein the cell membrane protein is a transporter protein, and the method comprises detecting an increase in the concentration of said transporter protein expressed at the surface of the target cell when agonist is present compared with when said agonist is absent.

71. (Previously presented) A method according to Claim 67, wherein said detecting is performed by an assay employing immuno-histochemistry, flow cytometry, western blotting of

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isolated plasma membrane cell fractions, or intra- and extracellular assessment of transported material.

72. (Previously presented) A method according to Claim 67, wherein the cell membrane protein is a membrane channel protein, and the method comprises detecting an increase in the concentration of said membrane channel protein expressed at the surface of the target cell when agonist is present compared with when said agonist is absent.

73. (Previously presented) A method according to Claim 67, wherein said detecting is performed by an assay employing biochemical assessment of ion concentration in an isolated sample, electrophysiology of tissue, intra- and extracellular assessment of transported material, immuno-histochemistry, flow cytometry, or western blotting of isolated plasma membrane cell fractions.

74. (Previously presented) A method according to Claim 58, wherein the protease is a bacterial protein or a fragment thereof capable of cleaving a protein of the exocytic fusion apparatus of the target cell.

75. (Currently amended) A method according to Claim 74, wherein the bacterial protein is ~~selected from~~ a clostridial neurotoxin ~~or an IgA protease~~.

76. (Withdrawn) A pharmaceutical composition, comprising an agent, said agent comprising:

(a) a targeting moiety that binds the agent to a binding site on a target cell, said binding site undergoes endocytosis to be incorporated into an endosome within the target cell, and wherein the targeting moiety is an agonist that is capable of increasing exocytic fusion in the target cell;

(b) a non-cytotoxic protease or a fragment thereof, said protease or protease fragment is capable of cleaving a protein of the exocytic fusion apparatus of said target cell; and

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(c) a translocation domain that translocates the protease or protease fragment from within the endosome, across the endosomal membrane, and into the cytosol of the target cell.

77. (Withdrawn) A pharmaceutical composition, comprising an agent, said agent comprising:

(a) a targeting moiety that binds the agent to a binding site on a target cell, said binding site undergoes endocytosis to be incorporated into an endosome within the target cell, and wherein the targeting moiety is an agonist that is capable of increasing exocytic fusion in the target cell;

(b) a DNA sequence encoding a non-cytotoxic protease or a fragment thereof, said DNA sequence is expressible in the target cell and when so expressed provides a protease or protease fragment capable of cleaving a protein of the exocytic fusion apparatus of said target cell; and

(c) a translocation domain that translocates the protease or protease fragment from within the endosome, across the endosomal membrane, and into the cytosol of the target cell.

78. (Withdrawn) A composition according to Claim 76, wherein the agonist is capable of contacting the target cell and increasing secretion from said target cell compared with when the agonist is absent.

79. (Withdrawn) A composition according to Claim 76, wherein the agonist is capable of contacting the target cell and increasing the concentration of a cell membrane protein expressed at the cell surface of said target cell compared with when the agonist is absent.

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80. (Withdrawn) A composition according to Claim 79, wherein the agonist is capable of contacting the target cell and increasing the concentration of a cell receptor protein expressed at the cell surface of said target cell compared with when the agonist is absent.

81. (Withdrawn) A composition according to Claim 79, wherein the agonist is capable of contacting the target cell and increasing the concentration of a transporter protein expressed at the surface of said target cell compared with when the agonist is absent.

82. (Withdrawn) A composition according to Claim 79, wherein the agonist is capable of contacting the target cell and increasing the concentration of a membrane channel protein expressed at the surface of said target cell compared with when the agonist is absent.

83. (Withdrawn) A composition according to Claim 76, wherein said agent has been prepared by a method according to Claim 58.

84. (Withdrawn) A composition according to Claim 76, wherein said agonist has been identified by a method according to Claim 60.

85. (Withdrawn) A composition according to Claim 76, further comprising an inhibitor that alleviates, in a patient, clinical symptoms caused by exocytic fusion in said target cell.

86. (Withdrawn) A composition according to Claim 85, wherein the inhibitor alleviates the clinical symptoms caused by increased exocytic fusion resulting from binding of the agonist to the target cell.

87. (Withdrawn) A composition according to Claim 85, wherein the inhibitor has a short-acting duration once administered to a patient, wherein the short-acting duration is 1-3 days.

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88. (Withdrawn) A composition according to Claim 76, wherein the protease is a bacterial protein or a fragment thereof capable of cleaving a protein of the exocytic fusion apparatus of the target cell.

89. (Withdrawn) A composition according to Claim 88, wherein the bacterial protein is selected from a clostridial neurotoxin or an IgA protease.

90. (Withdrawn) A DNA construct encoding the agent of Claim 76, said construct comprising a DNA encoding the targeting moiety or the translocation domain, and the protease or fragment thereof.

91. (Withdrawn) A method of preparing the agent of Claim 76, comprising expressing the DNA construct of Claim 90 in a host cell.

92. (Withdrawn) A method of preparing the agent of Claim 76, comprising covalently linking the targeting moiety or translocation domain, and the protease or fragment thereof.

93. (Withdrawn) A method of preparing the agent of Claim 77, comprising covalently linking the targeting moiety or translocation domain, and the DNA sequence encoding the protease or the fragment thereof.

94. (Withdrawn) A method for treating a medical disease or condition caused by exocytic fusion in a target cell, comprising administering to a patient a composition according to Claim 76.

95. (Withdrawn) A method according to Claim 94, wherein the composition is administered to a patient prior to, simultaneously with, or subsequent to an inhibitor, wherein the inhibitor alleviates, in the patient, clinical symptoms caused by exocytic fusion.

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96. (Withdrawn) A method according to Claim 95, wherein the inhibitor alleviates, in the patient, clinical symptoms caused by increased exocytic fusion resulting from binding of the agonist to the target cell.

97. (Withdrawn) A method according to Claim 95, wherein the inhibitor has a short-acting duration once administered to the patient, wherein the short-acting duration is 1-3 days.

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